Silica-supported chiral imidazolidinones as organocatalysts in stereoselective reactions under flow conditions

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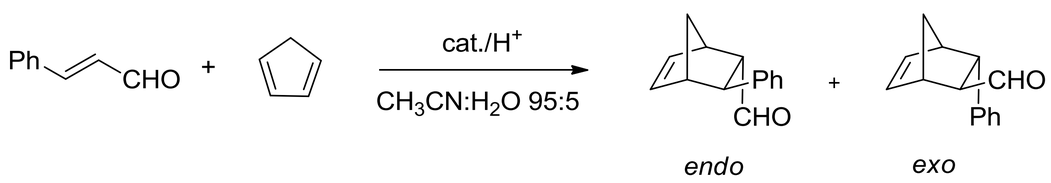
ABSTRACT

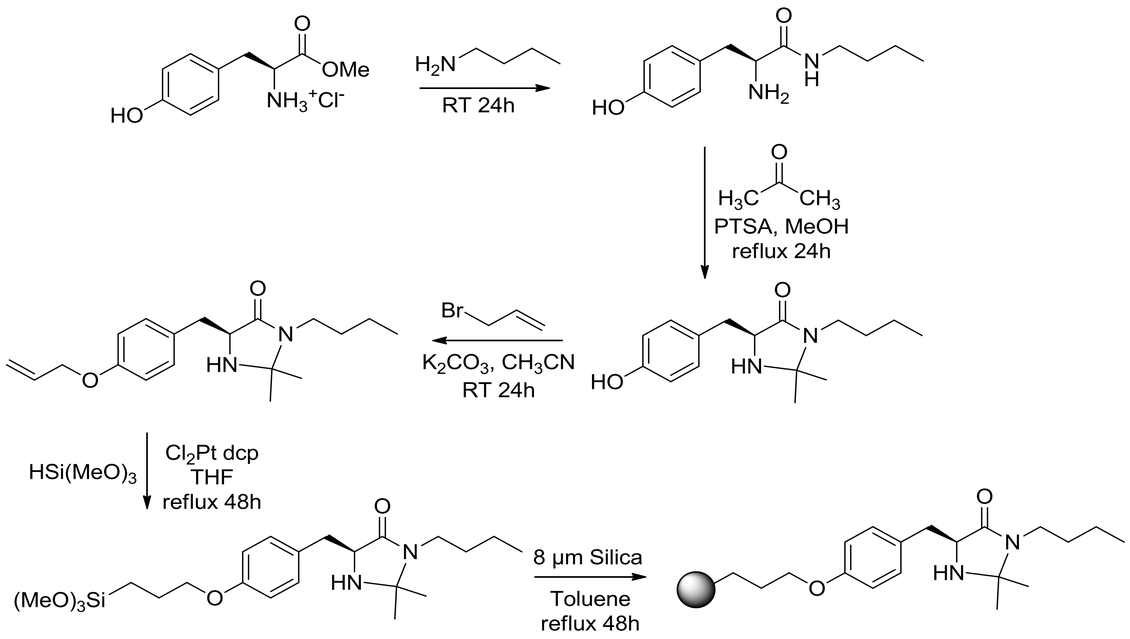
The so called MacMillan imidazolidinone organocatalysts are suitable for many stereoselective reactions undergoing through the formation of the iminium ion as activated species.[1] Given its popularity, it is not surprising that it has been covalently immobilized both on soluble[2] and insoluble supports.[3]
The use of the (*S*)-tyrosine-derived imidazolidinone anchored on silica as organocatalyst under flow chemistry conditions is described for the first time in this work. An HPLC column filled with the silica-supported catalyst was tested in the enantioselective Diels-Alder cycloaddition of cinnamaldehyde with cyclopentadiene. In comparison with batch conditions the process showed to be time saving maintaining both a good chemical activity and enantioselectivity for a long period of time, facilitating the isolation of the final product and avoiding the recovery step of the catalyst.

STEREOSELECTIVE DIELS-ALDER CYCLOADDITION

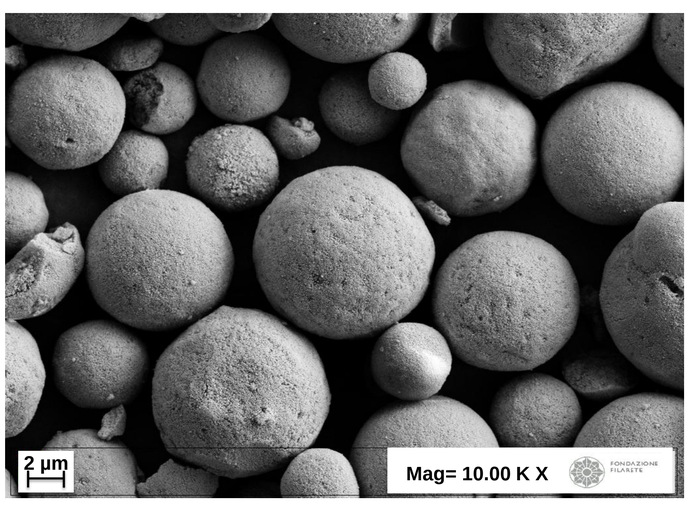


CATALYST

The MacMillan imidazolidinone catalyst functionalized with a proper linker was grafted onto 8 µm commercial silica.



Scanning Electron Micrograph (SEM) of the functionalized 8µm silica



RESULTS

FLOW CONDITIONS

Columns charged with fresh reagents every 48 hours

Salification of the catalyst with HBF_4 prior to filling the HPLC column:

Entry	Recovery time (h)	T (°C)	Flow rate (µL/min)	Residence time (h)	Conv.*(%)	e.e. endo (exo) (%)**
1	0-24	RT	5	10	55	39 (58)
2	24-30	RT	5	10	90	66 (70)
3	30-50	RT	3	16,5	96	83 (81)
4	50-56	0	3	16,5	98	87 (82)
5	56-75	0	3	16,5	79	84 (82)
6	75-144	RT	2	25	93	81 (78)

Salification of the catalyst with trifluoroacetic acid under flow conditions:

Entry	Recovery time (h)	T (°C)	Flow rate (µL/min)	Residence time (h)	Conv.*(%)	e.e. endo (exo) (%)**
1	0-24	RT	2,5	10	94	85 (85)
2	24-96	RT	2,5	10	64	77 (81)
3	96-120	RT	2,5	10	51	68 (70)
4	120-139	RT	2,5	10	57	69 (70)
5	139-158	RT	2,5	10	60	74 (72)

BATCH CONDITIONS

Salification of the catalyst with HBF_4 (RT)

Reaction time (h)	Conv.* (%)	e.e. endo (exo) (%)**
24	52	n.d.
48	78	78 (77)
Catalyst recycle (fresh reagents)		
72	5	n.d.
96	5	n.d.

Salification of the catalyst with trifluoroacetic acid (RT)

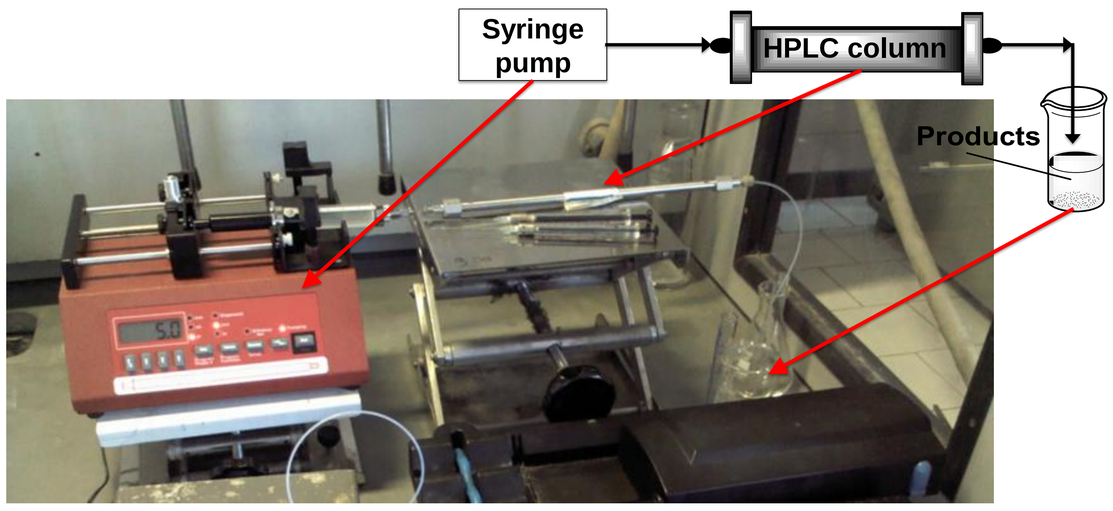
Reaction time (h)	Conv.* (%)	e.e. endo (exo) (%)**
24	46	n.d.
48	66	83 (86)
Catalyst recycle (fresh reagents)		
72	5	n.d.
96	5	n.d.

* Conversion based on ^{1}H-NMR spectra
** Enantiomeric excess determined by HPLC on chiral stationary phase after reduction with $NaBH_4$

CONTINUOUS FLOW REACTOR

Flow *vs* batch conditions:

- **Chemical activity and enantioselectivity maintained for a longer period of time**
- **Workup not necessary and easy isolation of the final product**
- **Avoided recovery and regeneration step of the catalyst**
- **Prolonged catalyst life**



[1] K.A. Ahrendt, C. J. Borths, D. W. C. MacMillan, J. Am. Chem. Soc. 2000,122, 17, 4243–4244

[2] M. Benaglia, G. Celentano, M. Cinquini, A. Puglisi, F. Cozzi, Adv. Synth. Catal. 2002, 344, 149-152. See also: S. Guizzetti, M. Benaglia, J. S. Siegel, Chem. Commun., 2012, 48, 3188-3190

[3] S.A. Selkälä, J. Tois, P.M. Pihko, A.M.P. Koskinen, Adv. Synth. Catal. 2002, 344, 941-945. See also: Y. Zhang, L. Zhao, S.S. Lee, J.Y. Ying, Adv. Synth. Catal. 2006, 348, 2027-2031